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By Kelly Rae Chi

Sizing up Nanoparticles

How to put nanoparticles to work in drug development.

Nanoparticles are increasingly found in drug development. Researchers are using them in designing treatments for tumors, infections, and brain diseases, as well as for imaging techniques that enhance visualization of molecular-scale events in brain tissue and culture dishes. But so far, says biochemist Michael Sailor of the University of California-San Diego, the technology for designing nanoparticles "is kind of like where we were when we were building Model T cars."

Creating nanoparticles—which are usually between 1 and 100 nanometers long and made from a variety of materials—and putting them to work within complex biological systems can be quite a challenge and it's not something scientists, especially newbies, do alone. Rather, the field of medical nanotechnology requires expertise from material scientists, engineers, and biologists, says Sailor. There are a number of parameters to play with. For example, researchers might

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see that they can alter their particles' shapes and sizes through simple changes to their preparation steps. These can lead to better targeting to the right organs, or extended release of a drug. Alternatively, scientists might be able to combine two less-than-stellar nanoparticle techniques to create a synergistic system. Maybe they'll need to create an entirely new nanoparticle, ideally one that's biodegradable if you eventually plan to use it in humans. These challenges require patience, but if done right, the quantity of nanoparticles produced can be easily scaled up.

The Scientist spoke with four researchers on the cutting edge of nanoparticle design. Here's what they said about the challenges and opportunities nanoparticles bring to drug development.

Shape Shifting

Project: Designing nanoparticles to treat infectious diseases

User: Padma Devarajan, Professor of Pharmaceutical Sciences and Technology, University of Mumbai, India

Problem: The spleen, a potential target in treating diseases such as splenic tuberculosis, AIDS, and malaria, receives only about 15% of nanoparticles injected into the bloodstream. That's because nanoparticles are rapidly cleared by immune cells within the liver before they reach the spleen. Devarajan wanted to create particles that bypassed the liver.

Solution: Her group stumbled onto a solution in 2008 when they were attaching the antibiotic drug doxycycline to lipid-polymer nanoparticles. By simply increasing the concentration of glycerol monostearate during the process of mixing together the nanoparticles with the drug, they produced two seemingly different types of particles that behaved differently: One lingered in the liver, as expected, but the other bypassed the liver and collected in the spleen. A closer look revealed that the nanoparticles targeting the spleen were irregularly shaped and made with greater concentrations of glycerol monostearate, whereas the ones in the liver were spherical. Data from their work and other labs suggested that the particles' shape determined whether they targeted the spleen (*J Biomed Nanotech* 4:359-66, 2008).

They then tagged the nanoparticles with a radiolabeled dye and observed their biodistribution in vivo. They found high splenic uptake in rats, rabbits, and especially dogs, whose spleen-to-liver uptake ratio was nearly 6, compared to 0.5 for the original preparation (*J Pharm Sci* Jan 20, 2010 Epub ahead of print). "We are currently evaluating methods to standardize the process," Devarajan says.

Considerations: In the past 2 years, scientists have shown that shape plays an important part in nanoparticle design. Devarajan says researchers should try tweaking simple steps in their nanoprecipitation protocols to see whether it helps targeting. Stick with simple, inexpensive methods: "When I am looking at a drug or therapy I should have something that could be scaled up easily; otherwise, it's no use," she notes.

Cooperative Particles

Project: Nanoparticle design for cancer diagnosis and therapy

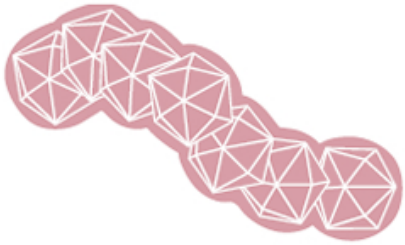
User: Michael Sailor, Professor of Chemistry and Biochemistry, University of

California–San Diego

Problem: Heating a tumor has shown some potential in treating cancer, but as a therapy it is somewhat nonspecific and inefficient. One approach is to use radiowaves, but small tumors do not convert the waves into heat efficiently. "You can get the tumor hot but not hot enough to kill it," Sailor says.

In a separate project, Sailor and his team found that when they inject worm-shaped nanoparticles with magnetic properties—called magnetic nanoworms—or liposomes containing tumor-targeting chemistry, relatively few of these particles actually made it to the tumor. His group needed a way to improve the specificity of their nanoparticles.

Solution: Sailor's group, in collaboration with Sangeeta Bhatia at the Massachusetts Institute of Technology and Erkki Ruoslahti at the Burnham Institute for Medical Research in La Jolla, Calif., came up with a new two-pronged approach to improve specificity of nanoparticles. The first step is injecting a gold nanorod, which accumulates in tumor blood vessels and makes the tumor more sensitive to laser heating than surrounding healthy tissue. The laser heat then changes the chemical composition of the tumors, making them express p32 receptors, a sign that the cells are stressed.



In the second step they injected a different type of nanoparticle—either magnetic nanoworms or liposomes loaded with the cancer chemotherapy drug doxorubicin and decorated with a nine-amino acid peptide called LyP-1, which is known to bind to p32 receptors. The particles were drawn to the tumors more readily when they were heated, and thus chemically altered, than when they weren't, according to the group's in vivo mouse studies (*PNAS* 104:981–86, 2010). "By separating the functions of two nanoparticles we could do better [reducing tumor size] than either of those two alone," Sailor says.

Considerations: The applicability of gold nanorods for tumor targeting is limited to near-surface tumors like skin cancer, but Bhatia's group has since found that attaching a substrate for an enzyme found in tumors to the nanorod in the first step keeps it in the body longer and improves its access to tumors.

Cleaving Chitosan

Project: Designing nanoparticles for extended-release drug delivery to the eye

User: Hong-Ru Lin, Professor of Chemical and Materials Engineering, Southern Taiwan University, Tainan

Problem: In 2005, Lin's group began altering nanoparticle drug carriers in eye drops to treat diseases like glaucoma. They created a nanoparticle containing a combination of chitosan, which is a linear polysaccharide, and polyacrylic acid (PAA). The group found that the drug pilocarpine, an established treatment for glaucoma, takes 315 minutes to clear out of the eye. In contrast, commercial drops containing pilocarpine take 90 minutes (*J Biomater Sci Polym Ed* 18:205–21, 2007).

Because of its versatile chemistry, chitosan is an increasingly popular nanoparticle choice for carrying drugs, vaccines, and DNA.

But there was one issue with the chitosan-PAA mix when they tested it in a culture dish of tear-like solution and in rabbits: When it hit a physiological pH of 7.4, the nanoparticles tended to precipitate. Lin's group needed a way to improve the solubility.

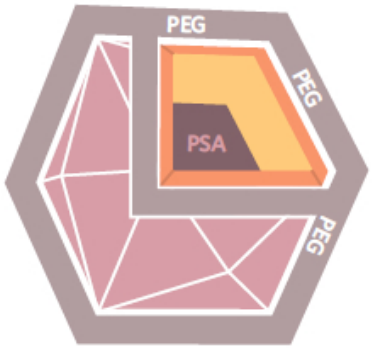
Solution: Chitosan is a large molecule, which affects its solubility. When Lin's group cleaved strings of polysaccharides with a hydrogen peroxide solution, the smaller version of the molecule still bound PAA. An in vivo study showed that the more soluble, modified nanoparticle delivered the drug at the same rate as the nonmodified one.

Lin showed the nanoparticles' loading efficiency—the percentage of drug that attaches to the nanoparticle—is roughly 70%. "In nanoparticle research, that's considered high," Lin says.

Considerations: Because of its versatile chemistry, chitosan is an increasingly popular nanoparticle choice for carrying drugs, vaccines, and DNA. There are several published methods for assembling chitosan nanoparticles. If you're still running into problems with precipitation, tweak reaction time, hydrogen peroxide concentration or temperature. (Lin used a 2M H_2O_2 solution, a reaction time of 2 hours, and a reaction temperature of 60 °C.) Higher temperatures degrade the electrostatic bonds within a chitosan molecule, causing an increase in the molecule's size.

As chitosan-PAA nanoparticles are nontoxic and biodegradable, they can be used for oral delivery. And because the pH of the gastrointestinal tract is lower than the physiological pH, you won't need to modify chitosan.

Penetrating Mucus



Project: Designing nanocarriers that penetrate human mucus barriers

User: Justin Hanes, Professor of Ophthalmology, Johns Hopkins University, Baltimore, Md.

Problem: Human mucus is about 2000-fold more viscous than water and turns over quickly, making the administration of nanoparticles through the eyes, nose, intestines, and cervix a long-standing challenge in drug development. "When you look at the viscosity, you might think it's impossible," says Hanes.

In 2007, his group described a latex nanoparticle that could penetrate the barrier. The key component was its outer coating of polyethylene glycol (PEG), a nontoxic material commonly used in pharmaceuticals (*PNAS* 104:1482–87). But having solved one problem, they created two others: their inner latex particles could not release drugs, and they are not degraded by the human body.

Human mucus is about 2000-fold more viscous than water.

Solution: Keeping the outer coating of PEG, Hanes' group developed a new type of inner particle composed largely of polysebacic acid (PSA), which traps therapeutic agents inside. They chose PSA because it has a unique degradation profile that provides steady release that can be tweaked from hours to weeks, and because it is efficient at encapsulating pH-

sensitive drugs.

In a recent study, the group showed that the new particles can be loaded with several different cancer drugs, and that a single dose of drug-loaded particles limited tumor growth in a mouse model of lung cancer for up to 30 days (*Biomaterials* 31:339-44, 2010).

Considerations: Hanes's group has patented its method, but Hanes says he's happy to give pointers to researchers who are interested in making their own PSA-PEG nanoparticles. He suggests sticking with low-molecular-weight PEG and applying a thick coat of it. He finds that if the coating is made of high-molecular-weight PEG or if it isn't sufficiently applied, the nanoparticle will get caught in the mucus.

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